Remarks

Reconsideration of the allowability of the present application is requested respectfully.

Status of the Claims

Claims 1, 2 and 21 to 44 are pending. No claim has been amended, cancelled, or added.

Summary of the Examiner's Action

The Examiner's Action consists of a Section 103(a) rejection, as summarized immediately hereafter, and an objection to the specification and a Section 112 rejection as discussed in other sections of this Reply.

All of the claims acted on by the Examiner have been rejected under 35 U.S.C. §103(a) as being unpatentable over the disclosure of British Patent No. 1,564,039 (hereafter "the Berger patent") in view of the disclosure of Patel et al., *Molecular Pharmacol.*, 46: 943-48 (1994) (hereafter "Patel et al.") and EPO 391,369 (hereafter "EP'369") and in further view of Woodruff et al. (Abstract), and U.S. Patent No. 5,223,507 to Dappen et al. (hereafter "Dappen et al.").

It is submitted respectfully that the Examiner's rejection is in error and should be withdrawn for reasons expressed below.

Discussion of the § 103 Rejection

The § 103 Rejection is traversed respectfully.

With all due respect to the case law cited in the Examiner's Action on pages 3 and 4, the fact is that the MPEP § 2143 sets forth the mandate for the propriety of establishing a *prima facie* case of obviousness. The mandate is that it must be shown that: (A) there is some suggestion or motivation, either in the cited documents themselves or in the knowledge of those skilled in the art, to modify or combine the cited disclosures; (B) there must be a reasonable expectation that the modification or combination of the cited disclosures would lead to a successful result; and (C) the combined disclosures must teach or suggest all of the elements of the claim. All three of these requirements must be satisfied for the Examiner to establish properly a *prima facie* case of obviousness. If any one such requirement is not satisfied, then the Examiner must withdraw the rejection.

It is submitted respectfully that none of the requirements set forth above exists in the present situation, as discussed below.

In the first instance, it must be recognized that the composition described in the primary reference (the Berger patent) and applicant's claimed composition are distinctly different and stem from different goals which each of the inventors was striving to achieve. The goal of Berger was to find a way to make α,d-propoxyphene (a known opioid analgesic) more effective as an analgesic because it is not addictive. Berger's development comprises formulating α,d-propoxyphene

with certain benzodiazepines which are tranquillizers that act on the receptor for the inhibitory neurochemical GABA to enhance its actions. Thus, Berger states the following.

> Generally, an analgesic effect is obtained by employing any of the benzodiazepines in the normal dosage amounts for the particular benzodiazepine employed when used as a tranquilliser. (page 3, lines 56-60 of the Berger patent)

The benzodiazipines disclosed by Berger for use in his development are 1,4-substituted compounds.

In distinct contrast, the claimed composition of the present invention includes an opioid-potentiating amount of a CCK antagonist, that is, a compound which possesses potent and direct antagonistic actions on CCK receptors. The CCK antagonists of the present invention comprise various classes of compounds, including benzodiazipines. Although it is acknowledged that Woodruff et al. disclose that medazepem is a CCK antagonist, the fact is that the art recognizes that this tranquillizer is not a compound suitable for use as "...an opioid-potentiating amount of a CCK antagonist..." (as set forth in applicant's claim 1). Note that the Berger benzodiazipines are 1,4-substituted compounds, as mentioned above, whereas the exemplary benzodiazipines of the present invention are 3-substituted, 1,4-substituted compounds. Accordingly, "benzodiazipines" included within the scope of the present claims belong to a different pharmacological class of compounds and have distinct chemical features which distinguish them from the 1,4-substituted compound disclosed in the Berger patent.

As such, the compounds disclosed in the Berger patent are suitable for

use as tranquilizers and one skilled in the art would recognize that they are not suitable for effective use as CCK antagonists. Furthermore, the Berger patent does not disclose the use of compounds described therein in a opioid-potentiating amount.

Accordingly, it is abundantly clear that, assuming *argumendo*, one skilled in the art would be motivated to combine the disclosures of one or more of the secondary references with the disclosure of the primary reference, the combined disclosures would not lead to applicant's claimed composition because the combined disclosures would not teach or suggest a composition which includes an opioid-potentiating amount of CCK antagonist. Thus, aforementioned requirement (C) of the "*prima facie*" mandate does not exist in the present situation.

As recognized by the Examiner, the primary reference does not disclose a composition which contains applicant's claimed biphasic carrier. The biphasic carrier is an important aspect of the present invention in that it provides the means by which water-soluble opioids and lipid-soluble CCK antagonists may be delivered simultaneously in a formulation which contains them. Keeping in mind that there is no disclosure whatsoever in the primary reference concerning a biphasic carrier and that there is no disclosure in any of the secondary references concerning a biphasic carrier, as will be pointed out hereafter, it is abundantly clear that there is no information of record that constitutes a suggestion or motivation that the disclosures of the references be combined or that one would be led to modify the composition of the primary reference in the manner proposed by the Examiner. Accordingly, aforementioned requirement (A) of the "*prima facie*" mandate does not exist in the present situation.

The Patel et al. reference discloses that CCK antagonists, such as devazepide, are poorly soluble, a fact disclosed in the present specification. There is no information in this reference respecting a biphasic carrier. Applicant is at a loss to understand the reason for this publication's being cited as a reference in view of the disclosure in the present specification concerning solubility characteristics of CCK antagonists.

EP '369 discloses a pharmaceutical composition of hydrophobic drugs in the form of oil-in-water emulsions having long term stability. This reference, however, does not disclose a composition which includes both water-soluble and water-insoluble drugs. This reference describes the use of a stable oil-in-water emulsion formulation as a means for delivery of only a hydrophobic drug. There is no disclosure of the emulsion's being used simultaneously as a carrier for a combination of water-soluble and water-insoluble pharmaceutically active agents. In addition, the primary reference does not disclose emulsions.

Dappen et al. discloses that gelatin, alginates, cross-linked carboxymethylcellulose and other celluloses, PVP, lactose, and other non-toxic compatible substances are known to be suitable excipients for pharmaceutical dosage forms containing opioids. Although this is clearly the case, this reference provides little more than a theoretical discussion of a particular field of chemistry and does not disclose pharmaceutical formulations. The possible inclusion of other pharmaceutical agents is mentioned, but it is not stated what these pharmaceutical agents are. Dappen et al. does not teach the skilled worker how to formulate a composition containing a water-soluble opioid and lipophilic compound. It is requested respectfully that the Examiner explain what the disclosure of Dappen et al.

adds to the disclosure of the primary reference in the context of a determination of the patentability of applicant's claims.

If the Examiner persists in his Section 103 rejection, it is requested respectfully that he explain why one skilled in the art would be led to combine the disclosures of the references and why one skilled in the art would expect that the modification of the composition of the primary reference as proposed by the Examiner would lead to a successful result. This should aid in accelerating prosecution of the present application.

Reply to Incorporation by Reference Objection

The Examiner has objected to pages 5 to 7 of the specification as incorporating improperly "essential material" by reference to foreign patent publications and non-patent publications. In particular, the Examiner has requested that the specification be amended to include the description of CCK antagonists as such description, which is considered "essential", is incorporated presently by reference. Applicant acknowledges that the description of CCK antagonists is essential material. The term "essential material", according to MPEP § 608.01(p), is material which is necessary to describe the claimed invention, to provide an enabling disclosure of the claimed invention, or to describe the best mode of the invention.

Applicant submits respectfully that such essential material is set forth in the specification explicitly and independently of the disclosures of the cited publications.

Thus, the specification describes explicitly on page e, lines 16 to 18, CCK antagonists which generally are the subject of the claims and exemplary CCK antagonists on page 5, lines 18 to 21, page 6, lines 5 to 9, and page 7, lines 1 to 10. The CCK antagonists are described explicitly in the specification as compounds which potentiate the analgesic effects of the involved opioids and/or compounds which reverse or prevent patient tolerance thereto. Exemplary CCK antagonists that fall within the scope of the general CCK antagonist definition are those of formulae (I), (II), (III), and (IV), MK-329, L-365,260, L-369,466, L-741,528, and L740-093.

Material incorporated explicitly in the specification provides also an enabling disclosure of the claimed invention with regards to the CCK antagonist as the specification identifies explicitly the structures of specific CCK antagonists on page 6, lines 1, 5 to 9, and page 7, lines 1 to 7, namely those of formulae (I), (II), (III), and (IV), MK-329, L-365,260, L-369,466, L-741,528, and L740,093.

In addition, material incorporated explicitly in the specification describes the best mode with regard to the CCK antagonist as it identifies the structures of particularly preferred CCK antagonists on page 6, lines 5 to 9 and page 7, lines 1 to 10, namely those of MK-329, L-365,260, L-369,466, L-741,528, and L740,093.

In view of the above, it is submitted respectfully that it is not necessary to amend the specification as requested by the Examiner.

Discussion of the § 112 Rejection

This rejection is traversed respectfully. The specification includes the following teaching.

> Preferably, the CCK antagonist is incorporated into the organic phase, and more preferably into the glyceride derivative, and the opioid analgesic is incorporated into the hydrophilic phase. However, the present invention does not preclude having components (a) and (b) present in any combination in any phase of the carrier. (page 5, first paragraph)

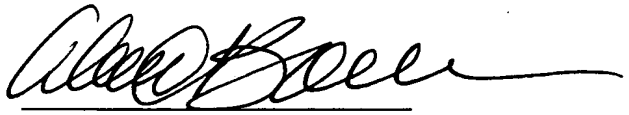
Accordingly, applicant's reference in the Reply dated July 15, 2002 is to a preferred embodiment of the applicant's invention and is not and was not intended to be inconsistent with the clear teaching of the specification as set forth in the above quotation.

Accordingly, it is requested respectfully that the Examiner's § 112 Rejection be withdrawn.

In view of the above, it is requested respectfully that the application be allowed in an early and favorable Action. As discussed with the Examiner during a conference by phone of even date, if the Examiner has reservations concerning allowing the application, it is requested respectfully that the Examiner phone the undersigned so that such reservations can be discussed, including discussion at a personal interview with the Examiner.

This Reply is accompanied by a Petition for Extending the Time to respond to the Examiner's Action.

Respectfully submitted,
Synnestvedt & Lechner LLP



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